Exhibit F

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DEBATE: TRANSVAGINAL MESH FOR POP – THE RECENT FDA UPDATE

Time to rethink: an evidence-based response from pelvic surgeons to the FDA Safety Communication: "UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse"

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Abstract In July of 2011 the U.S. Food and Drug Administration (FDA) released a safety communication entitled "UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse." The stated purpose of this communication is to inform health care providers and patients that serious complications with placement of this mesh are not rare and that it is not clear that these repairs are more effective than nonmesh repair. The comments regarding efficacy are based on a systematic review of the scientific literature from 1996–2011 conducted by the FDA. Our review of the literature during this time yields some different conclusions regarding the safety and efficacy of mesh use in prolapse repair. It may be useful to consider this information prior to making recommendations regarding mesh use in prolapse surgery according to the recent UPDATE.

Keywords Mesh · FDA · Transvaginal · Prolapse · Safety

This manuscript has been endorsed by over 600 members of the Pelvic Surgeons Network. A listing of the endorsing physicians of this commentary can be found at https://docs.google.com/leaf?id=0B1tkV5dMf-zIMjhjN2M4Y2ItMDNjMi00NmNmLWIzOWQtMTJmODkwMjY5YTA4&hl=en_US. Further contributions to this debate can be found at doi:10.1007/s00192-011-1580-3, doi:10.1007/s00192-011-1596-8, and doi:10.1007/s00192-011-1597-7.

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Introduction

This article was written in response to the recent Safety Communication UPDATE from the FDA regarding transvaginal placement of surgical mesh (TVM) for pelvic organ prolapse (POP). While the authors of this response agree with many of the points covered in the FDA's Safety Communication, we disagree with some of the conclusions and have concerns regarding the message that the UPDATE is sending to our patients and the healthcare community. We have divided our response into sections mirroring the format of the FDA UPDATE.

Regarding the section of the UPDATE entitled "Purpose"

In the UPDATE the FDA states, "The FDA is issuing this update to inform you that serious complications associated with surgical mesh for transvaginal repair of POP are not rare." The FDA News Release that accompanied the UPDATE states that in 2010 "at least 100,000 POP repairs that used surgical mesh" were performed and "about 75,000 of these were transvaginal procedures." This statement suggests that at least 225,000 TVM procedures are done in a 3-year period. In the 3-year period that this update addresses, there were "1,503 reports associated with POP repairs." Using these numbers the incidence of these reported complications is 0.67% (and the incidence may be even lower for TVM given that the news release states that "the reports don't always differentiate between transvaginal and abdominal procedures").

We realize that many complications of TVM go unreported to the MAUDE database and that the risk of complication with TVM is higher than 0.67%. However, the UPDATE implies that this risk of complication is higher than with native tissue repairs. Surgeons who perform native tissue repairs know that the risk of complications is certainly not <1%. In fact, when one of the more common native tissue repair techniques performed in the USA (the uterosacral ligament suspension) was first described, the risk of ureteral injury alone was 11% [1]. Since no FDA-monitored device is used in this and other native tissue repairs, it is difficult to know how many similar complications would be reported to the FDA if an alternative reporting mechanism were in place. Thus the assertion stated as the purpose of the UPDATE that TVM "may expose patients to greater risk" than traditional nonmesh repairs is unsupported.

The "Summary of problem and scope" of the UPDATE

This portion of the UPDATE focuses on a systematic review by the FDA of the literature published between 1996 and 2011. Our analysis of the randomized controlled trials (RCTs) and other large descriptive studies published during this time period lead to significantly different conclusions than were drawn by the FDA. In particular, the literature review led the FDA to draw four specific conclusions that we would like to address.

"Mesh used in transvaginal POP repair introduces risks not present in traditional non-mesh surgery for POP repair"

The UPDATE lists the following complications that have been reported to the FDA for TVM: mesh erosion, pain, infection, bleeding, pain during intercourse, organ perforation, and urinary problems. These risks do exist, and any patient who is considering a TVM surgery should be aware of them. However, they should also be aware that with the exception of mesh erosion, these are all risks of traditional nonmesh surgery as well. This statement implies that there are multiple risks of TVM that do not exist with traditional repairs. This is not accurate and is misleading to the public.

"Mesh placed abdominally for POP repair appears to result in lower rates of mesh complications compared to transvaginal POP surgery with mesh"

There is no question that mesh placed abdominally in the form of an abdominal sacral colpopexy (ASC) is an excellent procedure for treating POP. However, in the only published RCT comparing ASC to TVM, the authors failed to find a statistically significant difference in the rate of mesh erosion (they also failed to show a difference in quality of life measures) [2]. Nonetheless, most surgeons would agree that the risk of vaginal mesh exposure, in general, is higher when placed through the vaginal approach. In a comprehensive review of ASC, the authors report a 3.4% rate of mesh erosion [3], while in a similar review of TVM a rate of 10.3% was found [4]. However, it should be noted that surgical technique appears to play a significant role in the rate of mesh erosion, as these rates varied greatly between studies. In the TVM review, the rates vary from 0% to 29.7%. In fact, in one multicenter RCT of TVM, the rate of erosion between sites ranged from 0% to 100% [5]. Since the same mesh and delivery system were used in similar patient populations, it is reasonable to conclude that this variation is not a function of the mesh itself but rather the surgical technique.

Mesh complications are not the only complication patients are at risk for when undergoing surgical repair of POP. The risk of complications involving the abdominal wall (i.e., incisional hernia) and small bowel is almost certainly higher with ASC since the peritoneal cavity is traditionally not entered with TVM. Secondary analysis of one large RCT of ASC [6] concluded that one in 20 women

experiences significant gastrointestinal morbidity after ASC. More than half of most mesh exposures from TVM are asymptomatic, and one third need only minor outpatient operative intervention [5]. However, a small bowel obstruction following an open abdominal sacral colpopexy may require a second laparotomy and a prolonged inpatient admission. Thus while the rates of "complication" may be higher with TVM, the severity of the complications associated with ASC may be greater.

The UPDATE suggests that TVM does not result in better symptomatic (subjective) outcomes than traditional nonmesh repair. ASC is considered by many to be the "gold standard" procedure for POP; however, a recent Cochrane review [7] shows that there are only three published RCTs [8–10] comparing ASC to traditional nonmesh repair. Only one of these trials compared outcomes using validated quality of life instruments, and no difference in subjective success was noted [10]. We want to underscore that we are not trying to imply that traditional nonmesh repair and ASC are unsafe or ineffective procedures, we are simply suggesting that this singling out of TVM by the FDA seems arbitrary based on a lack of reporting systems for the other procedures.

"There is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh"

We agree that there is a relative paucity of comparative data regarding apical and posterior support with TVM, but we also feel that this issue is more complex than this statement implies. Of eight [5, 11–19] RCTs of TVM (using nonabsorbable mesh) vs nonmesh traditional surgery, only three were designed to investigate the apex as an outcome. All three failed to show a difference in the apex, but they also all lacked the statistical power to confirm that this failure was not the result of a type II error. One study [17] was halted prior to reaching the necessary sample size, and another [16] only had 14 subjects in the TVM arm. In fact, of the 287 subjects in these three trials, only six (2%) had apical failures. Therefore, apical failure (as defined in most RCTs) is not a very useful parameter to distinguish the anatomic success between POP procedures.

In regards to the posterior wall, again, we acknowledge that there are less data available compared to the anterior wall. Of the above-mentioned eight RCTs, only three [5, 15, 17] included the posterior compartment as an outcome. Contrary to the FDA's above statement, one of these three (a study of recurrent prolapse repair) did show superiority of mesh over nonmesh repairs in the posterior wall at 1 year of follow-up (4.1% failure in the mesh vs 24.5% in the nonmesh group, $P=0.003$) [5].

"While transvaginal surgical repair to correct weakened tissue between the bladder and vagina (anterior repair) with mesh augmentation may provide an anatomic benefit compared to traditional POP repair without mesh, this anatomic benefit may not result in better symptomatic results"

The primary outcome of six [11–15, 17, 18] of the seven [11–15, 17–19] existing RCTs on TVM vs traditional surgery for repair of the anterior compartment was anatomic cure. Of these six trials, only one failed to show superior anatomic correction of the anterior wall. These studies were not designed to detect differences in subjective outcomes but that does not mean that the objective outcomes should be discounted.

To detect statistically significant differences in symptoms at just 1 year after surgery requires different study parameters than a study designed to detect differences in anatomic results. The only study of these seven RCTs that used a composite primary outcome of anatomic and symptomatic results did show a difference in both outcomes [19]. This trial, published in the *New England Journal of Medicine*, randomized 410 subjects (twice as many subjects as the next largest study) to TVM vs standard anterior colporrhaphy. The composite primary outcome showed superior results for TVM at 2 months and at 1 year. The symptom of vaginal bulge between groups was not different at 2 months, but at 1 year, 37.9% of the colporrhaphy group vs only 24.6% of the TVM felt symptomatic bulging ($P=0.008$).

We therefore agree with the portion of the UPDATE that states, "mesh augmentation may provide an anatomic benefit compared to traditional POP repair without mesh"—but we find the statement "this anatomic benefit may not result in better symptomatic results" highly questionable. Given the current data, it would be equally true to state that "this anatomical benefit *may* result in better symptomatic results."

Erosion

Few specialists in the treatment of POP would argue that there are not some clinical scenarios (i.e., severe or recurrent prolapse) in which some type of graft-based repair is beneficial—whether that be done in a transvaginal or transabdominal approach. Across the board, the risk of mesh erosion might be higher with TVM; but in two large, multicenter trials conducted by surgeons who perform the index surgery on a regular basis, the results of the abdominal and vaginal approach are quite similar. In the TVM trial that randomized over 400 subjects, 3.2% had undergone a procedure to correct mesh erosion at 12 months [19]. In a well-known RCT of 322 women undergoing ASC, the erosion rate at 12 months was 4.3% (the number

needing intervention was not noted) [20]. We cannot emphasize enough that we are not attempting to denigrate sacral colpopexy in anyway. We are simply pointing out that mesh erosion is a risk any time mesh is used in reconstructive pelvic surgery and that surgical experience and technique play a significant role in the risk of erosion.

Mesh shrinkage, pelvic pain, and pain with intercourse

The UPDATE refers to mesh contraction (shrinkage) as a previously unidentified risk of TVM. While contraction may occur in some cases, analysis of translabial four-dimensional ultrasounds of 40 patients who underwent anterior mesh procedures showed no evidence of mesh contraction between their first and last postoperative visits [21]. This is only one imaging study, and the results have not yet been duplicated; however, we do have comparative clinical data. All but one [15] of the eight RCTs of TVM [5, 11–14, 16–19] measured pre- and postoperative vaginal length. None of these studies showed any difference in the change in vaginal length after surgery between the mesh and nonmesh arms of the studies. If there is shrinkage with TVM, it does not appear to affect vaginal length any more than does the trimming of the vaginal wall during standard colporrhaphy with native tissue.

In regards to pain with intercourse, one of the eight studies did not assess sexual function [16], but the remaining seven did. In one study, the dyspareunia score was significantly worse in the no mesh group at 2 years out [14]. In the others, no difference in sexual function was noted between the TVM and traditional repair groups [5, 12, 13, 15, 17–19].

Recommendations to health care providers from the FDA

We agree with and support the majority of the continued recommendations from the 2008 notification. Based on our review of the literature, however, we feel that the recommendations regarding the permanency of mesh and the risk of erosion apply to the placement of mesh regardless of whether it is being placed transvaginally or transabdominally for POP or as a treatment for incontinence. We also feel that the remainder of the recommendations (i.e., "Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse…") applies to nonmesh POP repairs as well.

We also agree with many of the new recommendations from the 2011 UPDATE. However, we question two of them. The first new recommendation, in particular, is misleading:

> Recognize that in most cases, POP can be treated successfully without mesh thus avoiding the risk of mesh-related complications.

The validity of this recommendation depends on how "most cases" is being defined. Studies show that traditional POP repairs can have high rates of failure [22, 23]. Factors such as patient age and severity of prolapse [24] can affect the chance of prolapse recurrence and should be taken into account when counseling patients. We agree that POP can be successfully treated without mesh in many cases, but not necessarily most. At the very least, a statement clarifying that success in treating anterior compartment and recurrent prolapse may be more likely with the use of mesh would lend balance to the FDA's communication.

We would also like to comment on one of the other new recommendations to health care providers in the 2011 UPDATE:

> Ensure that the patient understands the postoperative risks and complications of mesh surgery as well as limited long-term outcomes data.

We agree with this statement but would add that there is limited long-term data on all forms of prolapse repair. We would add that the limited long-term data that do exist on nonmesh repairs suggest a relatively high failure rate. Finally, there are long-term data on the transvaginal placement of mesh for urinary incontinence that does not show any untoward effects of mesh long term that were not present in the short term [25].

Conclusion

We recognize the FDA's mission to monitor manufactured devices in pelvic surgery and to advocate for patients' safety and best interests. The fundamental flaw in the FDA's analysis is that it is based on the question of proof of superiority of mesh in all patients. No one is suggesting that mesh is recommended for all patients. However, there may be instances when a surgeon suspects that a native tissue repair will have a high risk of failure and that the potential benefits of a mesh repair outweigh the risks.

The purpose of this response is to demonstrate that TVM is an important tool in our surgical armamentarium that may be the best option in some cases. From our vantage point, it appears that the FDA has presented a biased view of TVM among all POP repair procedures because of the current reporting mechanisms in place.

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